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ORIGINAL ARTICLE

Randomized trial of a comparison of the efficacy of TVT-O and single-incision tape TVT SECUR systems in the treatment of stress urinary incontinent women—2-year follow-up

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Abstract
Introduction and hypothesis The aim of this study was to compare the efficacy of the use of tension-free vaginal tape obturator (TVT-O) and single-incision TVT SECUR, hammock and U approach (TVT-S, H and U), in the treatment of urodynamic stress urinary incontinence (SUI).
Methods This single-center randomized three-arm trial compared the objective and subjective efficacy and early failure rate of the TVT-O and TVT-S H and U approach by objective criteria (cough test) and subjective criteria using the International Consultation on Incontinence Questionnaire—Short Form (ICIQ-UI SF). The objective efficacy rate was defined as the number of patients with a negative cough stress test. Subjective cure was defined by no stress leakage of urine after surgery based on the evaluation of ICIQ-UI SH (when patients ticked "Never"/"Urine does not leak" in answer to question 6: When does urine leak?). Objective and subjective efficacy were evaluated using Last Failure Carried Forward analysis, i.e., final analysis also included patients with early failure. To describe outcome at different time points, the Last Observation Carried Forward method was also implemented.
Results One hundred ninety-seven women with proven SUI were randomized into three groups—TVT-O (n=68), TVT-S H (n=64), and TVT-S U (n=65). Each patient allocated to a treatment group received the planned surgery. There were no differences in each group in preoperative characteristics. Median follow-up after surgery was 2 years (SD, 0.8; range, 0.1 to 3.8 years). Of the subjects, 92.6% in the TVT-O group, 68.8% in the TVT-S H group, and 69.2% in the TVT-S U group had negative stress test (p<0.001). Of the subjects, 85.3 % in the TVT-O group, 68.8% in the TVT-S H group, and 61.5% in the TVT-S U group were subjectively continent (p=0.02).
Conclusions Our study demonstrated a significantly lower subjective and objective cure rate in the single-incision TVT group compared to the TVT-O group.

Keywords Stress urinary incontinence · TVT-O · TVT-S · Surgical complication · Treatment failure

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Introduction

For years, efforts have been made to find an optimal operative procedure for stress urinary incontinence (SUI) that

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would be minimally invasive and have the same effect as previous procedures with fewer complications. In 1995, Ulmsten and Petros described the tension-free vaginal tape (TVT) method [1], which is minimally invasive and has a comparable effect to Burch colposuspension [2]. Due to retropubic trajectory during the tape insertion, serious perioperative complications were reported, including injury of the major vessels and bowel injury—sometimes with fatal consequences [3–6]. Despite the relative rarity of such complications, efforts were then made to minimize the risk of them occurring at all. In 2001, Delorme described the placement of the tape via the transobturator route (TOT—transobturator tape outside-in). The next modification of the transobturator procedure was tape placement inside-out (TVT-O) [7]. Synthetic midurethral slings are at present considered the gold standard for surgical treatment of SUI [8], but they are associated with some complications.

Various studies indicate that transobturator tapes are as effective as classical retropubic modification, but with lower complication rates [9–11]. The complication which is most often mentioned after this procedure is transient groin pain; this generally resolves within 1 month. Pain occurs in 0.8–9.7% of cases and makes the postoperative period unpleasant for the patient [12, 13]. This pain is caused by the trajectory of the tape due to passage through the inner adductors. Persistent groin pain due to irritation of the obturator nerve is a rare complication, and the prevalence of persistent groin pain has not yet been established. In an attempt to further reduce the invasive nature of the procedure and the complication rate, a new generation of TVTs has been introduced, and these are known as minitapes or single-incision tapes. The first tape of this kind was the TVT SECUR (TVT-S). It was expected that these tapes would be less invasive, the surgical procedure would require fewer tissue dissections, and there would be less postoperative pain, while maintaining a similar degree of efficacy. This hypothesis was based on the fact that the midurethral sling is introduced from a single incision without passing the retropubic space (TVT-S U) or the obturator foramina and its related nerves and vessels (TVT-S H). The expected anchoring structure for the tape in the U position is the connective tissue of the urogenital diaphragm and, for the H position, it is the obturator internus muscle. The first published short-term results were promising, and the data showed similar efficacy as retropubic or transobturator tapes [14]. Subsequent studies show lower efficacy than was expected [15, 16], and several case reports describing serious bleeding after this procedure have been published [17–19].

The aim of this study was to compare the efficacy of the TVT-O and TVT SECUR systems, H and U approach (TVT-S), in the treatment of stress urinary incontinent women.

Material and methods

Between January 2007 and November 2009, 197 women with proven urodynamic SUI were included in the randomized trial. The study was approved by the local ethics committee. The recruitment period for the study started on November 2006 to October 2009. During the study period, 1,832 patients underwent urodynamic screening in our department, 711 of whom were indicated for surgical treatment for SUI. Of the 711, 408 were suitable for the study and 205 agreed with randomization and signed the informed consent prior to treatment (Fig. 1). At the preoperative consultation (approximately 6–12 weeks before surgery), all patients received information about the study and informed consent. All patients were admitted to the hospital 1 day before surgery; if they agreed with participation and signed the informed consent forms, they were included into the study. For randomization, the envelope technique was used, which was opened shortly before the procedure. Patients were randomized into three groups—TVT-O (n=68), TVT-S H approach (n=64), and TVT-S U approach (n=65). The patients were not blinded. Based on prestudy statistical calculations, it was indicated that the required sample size for final statistical analysis in each group was 65 patients (allocation ratio, 1:1:1). We calculated with a dropout rate of 10%, so it was planned to enroll 72 patients into each group. Interim analysis was not initially planned. However, after 2 years, at which time 149 patients were enrolled into the study (55 in TVT-O, 51 in TVT-S U, and 43 in TVT-S H), the failure rate in the TVT-S group was clinically more prevalent, and thus, the reason for the unplanned interim analysis. Differences in the cure rate were virtually the same, as was expected prior to the study, although this difference was not enough to reach statistical significance. The study was terminated after 3 years when the minimum number of patients needed for final statistical analysis was achieved. The study was only intended to find the differences in efficacy between the TVT-O and TVT-S groups.

The objective efficacy rate was defined as the number of patients with a negative cough stress test. Subjective cure was defined by no stress leakage of urine after surgery based on evaluation with the International Consultation on Incontinence Questionnaire—Short Form (ICIQ-UI SH; range, 0–21).

All patients underwent complete urogynecological investigation before the procedure (history, clinical examination, and urodynamics according to ICS recommendations and ultrasound examination [20]), and they completed the ICIQ-UI SF and I-QoL questionnaires. Surgery was offered in cases of failure of conservative therapy. Inclusion criteria were age over 18 years, signed informed consent, urodynamic SUI, and agreement with postoperative follow-up.

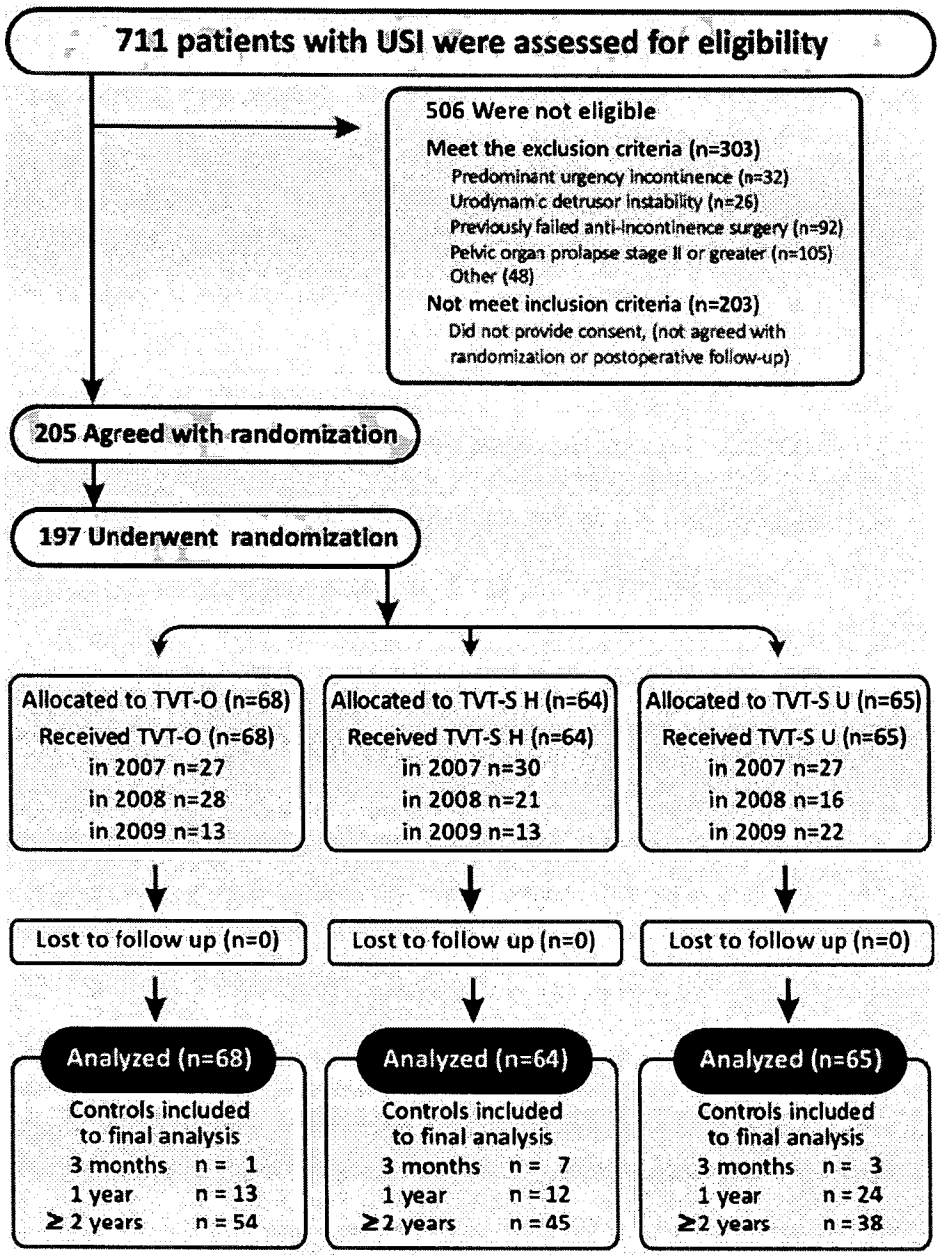

Fig. 1 Flowchart of participants through each stage of the study

Exclusion criteria were predominant urge incontinence, urodynamic detrusor instability, immobile urethra, previously failed anti-incontinence surgery, previous radiotherapy, postvoid residual volume (PVR) >100 ml, bladder capacity <300 ml, pelvic organ prolapse stage II or greater according to the International Continence Society Pelvic Organ Prolapse Quantification System, planned concomitant surgery, or age <18 years.

Surgical procedures

All surgical procedures were performed under general anesthesia with laryngeal mask airway. The patient was placed in the lithotomy position (90° between the table and the thigh), with a urethral catheter. Vaginal incision was initiated after infiltration with Supracain 4% (Zentiva, Prague, Czech Republic): one ampoule (2 ml) was diluted in 18 ml of water.

The TVT-O procedure (Ethicon Women's Health, Sommerville, NJ, USA) was performed according to the original technique described by de Leval [7]. To avoid excess tension during the plastic sheath removal, the Mayo scissors were placed between the tape and the urethra. Cystoscopy was not routinely performed for those patients.

The TVT-S procedure was performed according to the manufacturer's recommendations; this technique has been described previously [16, 21]. A sagittal vaginal incision of

approximately 1.5 cm was made after infiltration with Supracain 4% (Zentiva, Prague, Czech Republic): one ampoule (2 ml) was diluted in 18 ml of water.

After incision, the connective bridge was snipped at the 12 and 6 o'clock positions (undermining) so the tape could lie flat. Afterwards, paraurethral dissection using Mayo scissors was performed up to the lower level of the inferior ischiopubic ramus. Dissection was performed at the same angle as the planned insertion of the tape. The submucosal tunnel was checked to ensure there was enough space to allow placement of the device without dragging the paraurethral tissue. During placement of the tape in the H position, the needle driver and device were parallel to the pelvic floor and the device was rotated with the inserter tip at an angle of 45° from the patient's midline towards the ischiopubic ramus.

For the U position, the tip of the device was pointed upward; the needle driver was rotated from the sagittal midline (vertical plane) to aim the entire device towards the ipsilateral shoulder. Afterwards, the needle driver was lifted upright, so that the needle holder was in line with the vertical plane. For proper inserter placement, the ipsilateral index finger was located in the vaginal sulcus and, for forced application, the thumb was located on the inserter pad. The opposite hand on the needle driver provided directional guidance. We focus on adequate tensioning of a TVT-S sling so that the sling would be in direct apposition to the urethra.

During placement of the tape in the U position, the urethra and empty bladder were relocated to the contralateral side using a Foley catheter and rigid catheter guide. Cystoscopy was performed after each procedure, when the second inserter was placed.

The inserters were separated from the tape with the help of thin scissors which were placed between the inserter and the tape, without loosening the tape from the point of application [19]. In order to prevent the tape from being loosened from the fixation point, we avoided any shaking or rotating of the inserter during removal.

In all patients in both groups, a bladder catheter (16-Fr Foley) was kept in place for 24 h and vaginal packing for 12 h. After catheter removal, the postvoid residuum was measured by ultrasound or catheterization after spontaneous voiding (twice the minimum). When the PVR was >100 ml or there was complete retention, a Foley catheter was inserted for another 24-h period. If primary tape overcorrection was diagnosed (based on visible compression of the urethra at rest, abnormal kinking of the urethra at maximal Valsalva during ultrasound examination, or occlusion during urethral calibration), early tape release was provided. Using local anesthesia, the incision suture was cut, the tape was localized, thin scissors were placed between the tape and the urethra, and the tape was partially released (the tape was removed from direct contact with the urethra). Patients were discharged when the residual urine volume was <100 ml. Preoperatively, all patients received prophylactic antibiotic ampicillin + sulbactam 1.5 g i.v. (Unasyn, Pfizer, Prague, Czech Republic) or clindamycin 900 mg (Dalacin, Pfizer, Prague, Czech Republic) for those patients who were allergic to penicillin.

Any perioperative complications were monitored. Surgical evaluation included operating time (from incision to last suture), estimated intraoperative blood loss (vacuum aspiration), and perioperative complications (bladder perforation and vascular injury). Postoperative data were analyzed, including early postoperative complications (hematoma, spontaneous voiding recovery, and urinary tract infection) and late postoperative complications (procedure failure, tape erosion, and voiding difficulty).

Patients underwent a complete examination 3 months after surgery (similar to the preoperative examination). In addition, patients provided an evaluation of overall satisfaction with the surgical procedure using a Visual Analogue Scale (VAS; maximum, 100) and a five-item Likert scale (5—cured, very satisfied, 4—improved, satisfied, 3—no change to preoperative status, 2—worsened, not satisfied, 1—significantly worsened, not satisfied). The subsequent follow-ups were scheduled at 1 and 2 years after surgery (or 3 years, if the 2-year checkup was omitted), and the follow-up procedure was the same as at the 3-month follow-up, except for urodynamics. If the patient missed the follow-up appointment, they were contacted by phone or mail and another appointment was offered.

Postoperative follow-up was terminated if the surgery was deemed a failure. In these cases, reoperation was offered. For patients included in the study from January 2007 to December 2008, a minimum of 2 years control was required; for patients included in 2009, a 1-year control was required.

Criteria of cure and failure

The objective cure was defined as a negative cough stress test (urinary bladder filled to 300 ml of saline solution and the test performed in supine and standing positions).

Subjective cure was defined as no stress leakage of urine after surgery based on evaluation by a standardize questionnaire ICIQ-UI SH (patients ticked "Never"/"Urine does not leak" for question 6: "When does urine leak?"). Stress urinary leakage was registered if the patient ticked: "Leaks when you are physically active/exercising" or "Leaks when you cough or sneeze."

Urgency incontinence was registered if the patient ticked "Leaks before you can get to the toilet." Failure of the surgery was defined as subjective and objective failure or offer of reoperation.

Randomization and statistics

The sample size of the prospective randomized study was determined to be 195 women. Let us denote the probabilities

of successful surgeries in the three groups as $p_{TVT\text{-}O}$, p_H (TVT-S H), and p_u (TVT-S U). To compare these probabilities, we used the chi-square test of the hypothesis $p_{TVT\text{-}O}=p_H=p_u$. The sample size was derived from the requirement to detect actual probabilities (successful surgeries) $p_{TVT\text{-}O}=90\%$, $p_H=70\%$, and $p_u=70\%$ with the probability (power) of 80%. We determined the randomization sequence for assigning women to the three intervention groups (classical surgery—TVT-O, TVT-S H, TVT-S U). We implemented randomization by placing pieces of paper containing the randomization allocation in sealed envelopes which were arranged for sequential opening. We examined the women before and after surgery, and we performed a control examination 3 months, 1 year, 2 years, and 3 years after surgery.

Objective and subjective efficacy were evaluated using the Last Failure Carried Forward (LFCF) analysis, i.e., final analysis also included patients with early failure. The LFCF analysis carries forward a patient's last objective failure (e.g., 3 or 12 months) if their 12-, 24-, or 36-month test results are missing and also considers patients who had a subsequent reoperation for SUI as failures.

To describe outcome in different time points, the Last Observation Carried Forward (LOCF) imputation method was used. The last observed nonmissing value was used to fill in missing values at a later point in the study.

All statistical tests were performed at 5% level of significance. We used nonparametric Kruskal–Wallis one-way analysis of variance for quantitative features and Fisher's exact test for contingency tables. We used Bonferroni inequality to correct the p value in case of multiple comparisons.

Results

All women were Caucasians. There were no significant differences in age, body mass index (BMI), parity, or history of surgery for gynecological disorders among the study participants (Table 1). Preoperative urodynamic and QoL parameters were also not significantly different (Table 1). The mean age of the entire group was 56.5 years (SD, 10.0), mean BMI 26.9 kg/m^2 (SD, 4.5), mean parity 2.0 (SD, 0.8), mean ICIQ 14.9 (SD, 2.6) and I-QoL 53.8 (SD, 10.9), mean maximal urethral closure pressure (MUCP) 43.8 cm H_2O (SD, 16.8), and mean Qmax 27 ml/s (SD, 9.5).

Each patient allocated to her treatment group received the planned surgery (there was no need to convert planned surgery to another type). Using the intention-to-treat analysis, all randomized patients were analyzed.

There were no serious perioperative complications in the TVT-O group. In the TVT-S H group, there was one bladder perforation and two incidents of blood loss over 500 ml (one required transabdominal surgical revision of bleeding in the Retzius space). The mean blood loss in the TVT-O group was 24.9 ml (SD, 16.2), in the TVT-S H group 56.8 ml (SD, 129.1), and in the TVT-S U group 42.9 ml (SD, 22.9) (differences were statistically significant).

In the TVT-S H group during the procedure, two vaginal wall perforations were described. In two patients after TVT-O and one patient after TVT-S, prolonged urine retention occurred (all these patients underwent early tape release) (Table 2). Median follow-up after surgery was 2 years (SD, 0.8), minimum was 0.1 years and maximum was 3.8 years. The shortest follow-up was for a patient with early occurrence of failure. All failures were included in the final analysis. Time distribution of the controls included in the final analysis is in Table 4. We did not have 100% data from all planned controls (for example, the dropout rate at the 3-month control was 4.5%). Due to the organization of control and repeated offers of appointment, we were able to analyze data from all included patients. The length of follow-up is not different in the different groups, but in the TVT-S group, it is slightly shorter due to the higher prevalence of failure in these patients (Tables 3 and 4).

At the end of the study, objective and subjective assessment was significantly better in the TVT-O group compared to both TVT-S groups (Tables 3 and 5). Stress test was 92.6% negative in the TVT-O group, 68.8% in the TVT-S H group, and 69.2% in the TVT-S U group ($p<0.001$). The TVT-O group recorded a figure of 85.3% subjectively continent, while the figures for the other groups were 68.8% for the TVT-S H group and 61.5% for the TVT-S U group ($p=0.02$) (Table 5). Using the Likert scale, after TVT-O, 89.7% of patients evaluated their postoperative state as cured. In all studied groups, surgery significantly improved quality of life using the I-QoL and ICIQ questionnaires and VAS. There were no significant differences in overall satisfaction between the groups. Only the differences in the ICIQ results reached the level of statistical significance, again favoring the TVT-O procedure. Using the mean VAS for overall satisfaction with the procedures, there were no differences, although the number of satisfied patients with VAS over 90 was statistically significantly more prevalent in the TVT-O group.

De novo urgency was more prevalent in the TVT-O group, although the difference was not statistically significant. Urgency and urgency incontinence were reduced to the same degree in all groups.

In the TVT-S H group, 12 (18.7%) patients were assessed as failure, 8 of whom underwent further anti-incontinence procedures (Tables 4 and 5). In the TVT-S U group, failure occurred in nine cases (13.8%) and seven underwent further anti-incontinent procedures Tables 3 and 5. Two patients in the TVT-O group subjectively evaluated their status as worse than the preoperative status. They complained of de novo voiding symptoms [slow stream, straining to void, and feeling

Table 1 Preoperative patient characteristics

	TVT-O	TVT-S H	TVT-S U
Number	68	64	65
Age, years	56.6±9.7	55.2±10.2	57.7±10.1
BMI, kg/m^2	27.0±4.5	26.2±4.2	27.6±4.8
Parity	1.8±0.9	2.1±0.9	2.0±0.7
Prior hysterectomy, *n* (%)	19 (27.9%)	18 (28.1%)	16 (24.6%)
Mixed UI, *n* (%)	29 (42.6%)	25 (39.1%)	27 (41.5%)
Urgency, *n* (%)	41 (60.3%)	31 (48.4%)	32 (49.2%)
MUCP, cm H_2O	43.0±18.2	44.3±18.0	44.0±18.9
MUCP <20 cm H_2O, *n* (%)	7 (10.3%)	6 (9.4%)	6 (9.4%)
MUCP <30 cm H_2O, *n* (%)	17 (25%)	17 (26.6%)	17 (26.6%)
Maximum flow rate, ml/s	28.0±11.7	26.6±7.8	26.3±8.4
ICIQ	15.1±2.7	15.0±2.2	14.7±2.9
I-QoL	53.5±9.6	52.9±8.4	55.1±14.0

Values are given as the mean ± SD or number of patients (percent)

MUCP maximal urethral closure pressure

of incomplete emptying proven by uroflowmetry (maximum flow was below 5 centiles using the Liverpool nomogram)] with de novo urgency and urgency incontinence, but the recurrence of SUI was not noted. Both underwent tape cutting. Six patients in the TVT-O group complained of slow stream, versus one in the TVT-S U group and none in the TVT-S H group. In the TVT-S groups, the incidence of tape protrusion was also higher (although this was not statistically significant): in the TVT-S H group, there were five cases (7.8%) and, in the TVT-S U group, there were four cases (6.1%), compared to one in the TVT-O group (1.4%).

Implementation of LOCF analysis (Table 6) revealed decreasing subjective and objective efficacy in the TVT-S groups at different time points after surgery. For example, 3 months after surgery, the stress test was positive in 18% of the TVT-S H group and in 23.3% of the TVT-S U group. Three years after surgery, positive stress test was observed in 31.2% of women after TVT-S H and in 30.8% after TVT-S U procedures.

Discussion

The reason for the development of the single-incision tape was to offer patients a new procedure with the same efficacy as retropubic or transobturator tape but with lower complication rates. In fact, the success rate seems to be lower than for retropubic or transobturator tapes [2, 9]. In our randomized trial, we demonstrated lower efficacy of the TVT-S procedure compared to TVT-O. Stress test was negative in 92.6% in the TVT-O group, in 68.8% in the TVT-S H group, and in 69.2% in the TVT-S U group ($p<0.001$). The TVT-O group recorded 85.3% as subjectively continent, while the other groups recorded 68.8% for the TVT-S H and 61.5% for the TVT-S U ($p=0.02$). We did not demonstrate differences in the TVT-S group between the hammock and U approaches. For evaluation of the effect of surgery, we used different instruments. In virtually all monitored parameters, the results after TVT-S were inferior to those after the TVT-O procedure. We cannot

Table 2 Perioperative characteristics

	TVT-o	TVT-S H	TVT-S U	*p* value
Duration of procedure, min	8.3±3.5	10.8±4.4	11.4±3.7	<0.001[a]
Estimated blood loss, ml	24.9±16.2	56.8±129.1	42.8±22.2	<0.001[a]
Estimated blood loss >100 ml	1	2	2	NS[b]
Estimated blood loss >500 ml	0	2	0	NA[b]
Bladder injury	0	1	0	NA[b]
Urethral injury	0	0	0	NA[b]
Vaginal wall perforation	0	2	0	NA[b]
Postoperative urine retention (>24 h)	2	0	1	NA[b]
Urinary tract infection	6 (8.8%)	3 (4.5%)	4 (6.2%)	NA[b]
Early tape release	2	0	1	NA[b]

Values are given as the mean ± SD or number of patients (%)

NS not significant ($p>0.05$)

[a]Kruskal–Wallis χ^2 test

[b]Fisher's exact test

Table 3 Long-term subjective and objective follow-up, quality of life

	TVT-O	TVT-S H	TVT-S U	*p* value
Length of follow-up years	2.0±0.7	1.9±0.9	1.9±0.9	NS[a]
Number	68	64	65	
Subjective cure rates				
Cured (5)	61 (89.7%)	46 (71.9%)	51 (78.5%)	0.03
Improved (4)	5 (7.4%)	6 (9.4%)	7 (10.8%)	NS[b]
No change (3)	0	9 (14.1%)	6 (9.2%)	0.002
Worsened (1+2)	2 (2.9%)	3 (4.7%)	1 (1.5%)	NS[b]
ICIQ	2.8±3.6	4.9±5.8	4.6±4.9	0.055[a]
Subjective stress negative	58 (85.3%)	44 (68.8%)	40 (61.5%)	0.01
Subjective stress positive	10 (14.7%)	20 (31.2%)	25 (38.5%)	0.01
I-QoL	99.1±13.1	91.1±22.4	94.6±18.3	NS[a]
Urgency	30 (44.1%)	29 (45.3%)	24 (36.9%)	NS[b]
De novo urgency	13 (19.1%)	8 (12.5%)	5 (7.7%)	NS[b]
Urgency cured	14 (20.6%)	13 (20.3%)	15 (23.1%)	NS[b]
Urgency incontinence	15 (22.1%)	14 (21.9%)	15 (23.1%)	NS[b]
Urgency incontinence cured	10 (14.7%)	8 (12.5%)	7 (10.8%)	NS
VAS	94.4±12.9	80.4±34.7	85.4±24.8	NS[a]
VAS ≥90	64 (94.1%)	46 (71.9%)	50 (76.9%)	0.001[b]
Objective cure rates				
Stress test negative	63 (92.6%)	44 (68.8%)	45 (69.2%)	<0.001[b]
Stress test positive	5 (7.4%)	20 (31.2%)	20 (30.8%)	<0.001[b]
Failure	0 (0%)	12 (18.8%)	9 (13.8%)	0.0002[b]
Reoperation for SUI	0 (0%)	8 (12.5%)	7 (10.8%)	NA[b]
Tape cut	2 (2.9%)	0 (0%)	0 (0%)	NA
Tape erosion	1 (1.5%)	5 (7.8%)	4 (6.2%)	NA[b]
Chronic UTI	2 (2.9%)	0 (0%)	1 (1.5%)	NA[b]

Values are given as the mean × SD or number of patients (%)
NS not significant ($p>0.05$)
[a]Kruskal–Wallis χ^2 test
[b]Fisher's exact test

exclude the possibility that further decline in efficacy will occur in the TVT-S group over time, especially since we noted a decline in the success rate from the 3-month checkup to the end of the study. We noted several patients who were without problems 2 years after the surgery, but 1 year later they came back with recurrent SUI. By improving the insertion technique, we did increase the success rate compared to our initial results [21, 22], but the results still remain inferior to the other tape procedures like TVT or TVT-O. We started this study after performing approximately 100 TVT-S procedures in our department (by the same surgeon who provided all procedures in this study), so the results of this study were not influenced by the learning curve.

Table 4 Time distribution of the controls included in final analysis

	TVT-O	TVT-S H	TVT-S U	Total
3 months control	1	7	3	11
1 year control	13	12	24	49
2 or 3 years control	54	45	38	137
Total	68	64	65	197

The available published data indicate different results. Promising results with TVT-S have been published in one of the first studies, with a short-term failure rate of only 8% [14]. In that study, only telephone interviews were conducted to record responses to the questionnaire at 12 months postoperatively. Another multicenter prospective study with 15±3 months follow-up displayed subjective and objective cure rates of 78% and 81%, respectively [23]. Virtually identical results were published in another prospective randomized trial comparing the TVT-S U and H approach: objective cure rate for the U approach was 87.5% and for the H approach was 80.1% [24]. Those results are very similar to the short-term data from our randomized trial.

Different results with substantially lower cure rates have been published by other authors. Lim published short-term data from two tertiary referral urogynecological centers with a 6-month follow-up of 42 consecutive patients [25]. Objective and subjective cure rates in this study were 58.3% and 51.3%, respectively. Very similar results were published by Krofta, with an objective cure of 52.4% after 1-year follow-up [16]. The low cure rates in those studies may be influenced by the learning curve, and they were comparable to our initial results [21, 22]. In a larger prospective study, Debodiance [26]

Table 5 Comparison of each method for primary outcome

		TVT-O, *n* (%)	TVT-S H, *n* (%)	*p* value[a]	OR	95% CI
	Failure	0	12 (18.8%)	0.0003	Infinity	3.4–infinity
	STneg	63 (92.6%)	44 (68.8%)	0.002	5.7	1.9–20.8
	SSneg	58 (85.3%)	44 (68.8%)	0.11	0.4	0.1–1.0
		TVT-O, *n* (%)	TVT-S U, *n* (%)			
	Failure	0	9 (13.8%)	0.0035	Infinity	2.3–infinity
	STneg	63 (92.6%)	45 (69.2%)	0.002	5.5	1.8–20.3
	SSneg	58 (85.3%)	40 (61.5%)	0.0085	0.3	0.1–0.7
		TVT-S H, *n* (%)	TVT-S U, *n* (%)			
	Failure	12 (18.8%)	9 (13.8%)	1	0.7	0.24–1.98
	STneg	44 (68.8%)	45 (69.2%)	1	0.98	0.3–2.2
	SSneg	44 (68.8%)	40 (61.5%)	0.46	0.7	0.3–1.6

STneg stress test negative, *SSneg* subjective stress negative

[a] *p* value after Bonferroni correction

reported a 70.3% cure rate after a 1-year follow-up. Finally, in a well-designed prospective randomized blinded multicenter study comparing TVT and TVT-S, Andrada Hamer recorded 20% lower subjective cure rates 2 months after surgery, based only on telephone interviews [27].

Some authors have not established any differences in cure rate between the TVT-S and TVT-O procedures and claim high efficacy of 81.6% to 83.8%, respectively [28]. Other authors compared the efficacy of the three surgical methods at the 12-month follow-up and established a lower cure rate after TVT-S (67%), compared to TVT-0 (83%), with 87% after the miniArc [29].

Another midterm evaluation of TVT-S efficacy on a relatively small group of patients (n=45) reveals high failure, with a short-term cure rate of 93% declining to 40% after a mean follow-up of 30.2 months [30].

The higher failure rate of this procedure should be explained based on anatomical studies [31, 32]. In many cases, we are not able to reach the intended place for proper tape fixation with this inserter type. This problem may be due to the physiological variability of the individual structures in the lesser pelvis, and it is questionable whether the length of the minitape (8 cm) is appropriate for all patients.

Table 6 Comparison of each method for primary outcome at different time points from surgery using LOCF analysis

	Total	TVT-O	TVT-S H	TVT-S U	*p* value[a]
3 months after surgery					
Number	186	65	61	60	NA
SSpos		6 (9.2%)	11 (18.0%)	13 (21.7%)	NS
STpos		3 (4.6%)	11 (18.0%)	14 (23.3%)	0.0056
Failure		0 (0%)	7 (11.5%)	3 (5.0%)	0.009
1 year after surgery					
Number	192	66	62	64	NA
SSpos		5 (7.6%)	18 (29.0%)	23 (35.9%)	<0.001
STpos		4 (6.1%)	14 (22.6%)	20 (31.2%)	<0.001
Failure		0 (0%)	10 (16.1%)	7 (10.9%)	<0.001
2 years after surgery					
Number	197	68	64	65	NA
SSpos		8 (11.8%)	20 (31.2%)	24 (36.9%)	0.0017
STpos		5 (7.4%)	18 (28.1%)	20 (30.8%)	<0.001
Failure		0 (0%)	12 (18.8%)	9 (13.8%)	<0.001
3 years after surgery					
Number	197	68	64	65	NA
SSpos		10 (14.7%)	20 (31.2%)	25 (38.5%)	0.01
STpos		5 (7.4%)	20 (31.2%)	20 (30.8%)	<0.001
Failure		0 (0%)	12 (18.8%)	9 (13.8%)	<0.001

Values are given as the number of patients (percent)

STpos stress test positive, *SSpos* subjective stress positive

[a] Fisher's exact test

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Ridgeway et al. published a study that focused on the variability of the bony pelvis in which the interobturator foramina distance varied from 4.3 to 6.9 cm (mean, 5.7± 0.5). They concluded that there is considerable variability in the bony architecture of the obturator foramen and pubic arch of the female pelvis [33].

Another reason for failure may be the insertion technique: shaking and rotation with the tape inserter may destroy the place of fixation or leave the tape partially removed. In addition, the incidence of complications—especially hemorrhagic—is relatively high. A possible reason for hemorrhagic complications may be the scalpel-shaped tip of the inserter, which can cut the fibers of the obturator muscle [19] or vessels. In our study, we observed more complications after the TVT-S H approach: two cases of severe bleeding and one urinary bladder perforation. Other surgeons have described bleeding complications after the TVT-S U procedure because, for some patients, the inserter is long enough to reach vessels like the corona mortis [17, 18].

It is also important to discuss the limitations of our study. First, the study was only designed to detect primary outcome—efficacy in the treatment of SUI—and was not intended to find differences in secondary outcomes, such as effect on urgency incontinence and de novo urgency, and occurrence of other complications. Another weakness is that the study was only intended to find differences in efficacy between the TVT-O and TVT-S groups. The study was not designed to find differences between the two TVT-S groups. For this purpose, another study should be prepared with a higher number of participants. We proved lower efficacy in both TVT-S groups in comparison to TVT-O; therefore, further research in this field is controversial.

Because our trial excluded patients with pelvic organ prolapse and concomitant prolapse surgery, clinical outcomes for the treatment of SUI and significant prolapse conditions should not be extrapolated from these results. Lack of concomitant surgery and conducting the study in a single center also decreases generalizability of our study.

Other weaknesses of our study were that the patients were not blinded and groin pain after surgery was not monitored. The strength of this study is that it is a randomized study with longer than 1-year follow-up with standardized objective and subjective outcomes measurements in patients with uncomplicated SUI.

In our study, we used the LFCF method. It should be mentioned that most of the studies use the completer method, which evaluates the results of patients who have completed a follow-up visit. The LFCF method is more conservative in comparison to the completer analysis and carries forward failures. Finally, we also used the LOCF method which describes different outcome time points (3 months, 1 year, 2 years, and 3 years after surgery). This method described the trends and allows a more realistic view of the data.

It would be optimal to publish well-performed studies with adequate length of follow-up before the introduction of new or modified surgical procedures.

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References

1. Ulmsten U, Petros P (1995) Intravaginal slingplasty (IVS): an ambulatory surgical procedure for treatment of female urinary incontinence. Scand J Urol Nephrol 29:75–82
2. Ogah J, Cody DJ, Rogerson L (2011) Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. Neurourol Urodyn 30:284–291
3. Deng D, Rutman M, Raz S, Rodriguez L (2007) Presentation and management of major complications of midurethral slings: are complications under-reported? Neurourol Urodyn 26:46–52
4. Karram M, Segal J, Vassallo B, Kleeman S (2003) Complications and untoward effects of the tension-free vaginal tape procedure. Obstet Gynecol 101:929–932
5. Kuuva N, Nilsson C (2002) A nationwide analysis of complications associated with the tension-free vaginal tape (TVT) procedure. Acta Obstet Gynecol Scand 81:72–77
6. Flock F, Reich A, Muche R, Kreienberg R, Reister F (2004) Hemorrhagic complications associated with tension-free vaginal tape procedure. Obstet Gynecol 104:989–994
7. de Leval J (2003) Novel surgical technique for the treatment of female stress urinary incontinence: transobturator vaginal tape inside-out. Eur Urol 44:724–730
8. Nilsson C, Falconer C, Rezapour M (2004) Seven-year follow-up of the tension-free vaginal tape procedure for treatment of urinary incontinence. Obstet Gynecol 104:1259–1262
9. Novara G, Ficarra V, Boscolo-Berto R, Secco S, Cavalleri S, Artibani W (2007) Tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials of effectiveness. Eur Urol 52:663–678
10. Novara G, Galfano A, Boscolo-Berto R, Secco S, Cavalleri S, Ficarra V et al (2008) Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and different devices. Eur Urol 53:288–308
11. Richter HE, Albo ME, Zyczynski HM, Kenton K, Norton PA, Sirls LT et al (2010) Retropubic versus transobturator midurethral slings for stress incontinence. N Engl J Med 362:2066–2076
12. Meschia M, Bertozzi R, Pifarotti P, Baccichet R, Bernasconi F, Guercio E et al (2007) Peri-operative morbidity and early results of a randomised trial comparing TVT and TVT-O. Int Urogynecol J Pelvic Floor Dysfunct 18:1257–1261
13. Debodinance P (2007) Trans-obturator urethral sling for the surgical correction of female stress urinary incontinence: outside-in (Monarc)

versus inside-out (TVT-O). Are the two ways reassuring? Eur J Obstet Gynecol Reprod Biol 133:232–238
14. Neuman M (2008) Perioperative complications and early follow-up with 100 TVT-SECUR procedures. J Minim Invasive Gynecol 15:480–484
15. Liapis A, Bakas P, Creatsas G (2010) Comparison of the TVT SECUR System "hammock" and "U" tape positions for management of stress urinary incontinence. Int J Gynaecol Obstet 111:233–236
16. Krofta L, Feyereisl J, Velebil P, Otcenasek M, Kasikova E, Krcmar M (2010) TVT-S for surgical treatment of stress urinary incontinence: prospective trial, 1-year follow-up. Int Urogynecol J 21:779–785
17. Gobrecht U, Kuhn A, Fellman B (2011) Injury of the corona mortis during vaginal tape insertion (TVT-Secur using the U-Approach). Int Urogynecol J 22:443–445
18. Larsson PG, Teleman P, Persson J (2010) A serious bleeding complication with injury of the corona mortis with the TVT-Secur procedure. Int Urogynecol J 21:1175–1177
19. Masata J, Martan A, Svabik K (2008) Severe bleeding from internal obturator muscle following tension-free vaginal tape Secur hammock approach procedure. International Urogynecology Journal 19:1581–1583
20. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J et al (2010) An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecol J 21:5–26
21. Martan A, Svabik K, Masata J, Koleska T, El-Haddad R, Pavlikova M (2009) Initial experience with a short, tension-free vaginal tape (the tension-free vaginal tape secur system). Eur J Obstet Gynecol Reprod Biol 143:121–125
22. Martan A, Svabik K, Masata J, Koleska T, El-Haddad R, Pavlikova M (2009) Correlation between changes in ultrasound measurements and clinical curative effect of tension-free vaginal tape-SECUR* procedure. International Urogynecology Journal 20:533–539
23. Meschia M, Barbacini P, Ambrogi V, Pifarotti P, Ricci L, Spreafico L (2009) TVT-secur: a minimally invasive procedure for the treatment of primary stress urinary incontinence. One year data from a multi-centre prospective trial. Int Urogynecol J Pelvic Floor Dysfunct 20:313–317
24. Lee KS, Lee YS, Seo JT, Na YG, Choo MS, Kim JC et al (2010) A prospective multicenter randomized comparative study between the U- and H-type methods of the TVT SECUR procedure for the treatment of female stress urinary incontinence: 1-year follow-up. Eur Urol 57:973–979
25. Lim JL, de Cuyper EM, Cornish A, Frazer M (2010) Short-term clinical and quality-of-life outcomes in women treated by the TVT-Secur procedure. Aust N Z J Obstet Gynaecol 50:168–172
26. Debodinance P, Amblard J, Lucot JP, Cosson M, Villet R, Jacquetin B (2009) TVT Secur: prospective study and follow up at 1 year about 154 patients. J Gynecol Obstet Biol Reprod (Paris) 38:299–303
27. Andrada Hamer M, Larsson PG, Teleman P, Eten-Bergqvist C, Persson J (2011) Short-term results of a prospective randomized evaluator blinded multicenter study comparing TVT and TVT-Secur. Int Urogynecol J Pelvic Floor Dysfunct 22:781–787
28. Tommaselli GA, Di Carlo C, Gargano V, Formisano C, Scala M, Nappi C (2010) Efficacy and safety of TVT-O and TVT-Secur in the treatment of female stress urinary incontinence: 1-year follow-up. Int Urogynecol J Pelvic Floor Dysfunct 21:1211–1217
29. Oliveira R, Botelho F, Silva P, Resende A, Silva C, Dinis P et al (2011) Exploratory study assessing efficacy and complications of TVT-O, TVT-Secur, and Mini-Arc: results at 12-month follow-up. Eur Urol 59:940–944
30. Cornu JN, Sebe P, Peyrat L, Ciofu C, Cussenot O, Haab F (2010) Midterm prospective evaluation of TVT-Secur reveals high failure rate. Eur Urol 58:157–161
31. Hubka P, Masata J, Nanka O, Grim M, Martan A, Zvarova J (2009) Anatomical relationship and fixation of tension-free vaginal tape Secur. International Urogynecology Journal 20:681–688
32. Hubka P, Nanka O, Martan A, Grim M, Zvarova J, Masata J (2011) TVT-S in the U position-anatomical study. Int Urogynecol J 22:241–246
33. Ridgeway BM, Arias BE, Barber MD (2008) Variation of the obturator foramen and pubic arch of the female bony pelvis. Am J Obstet Gynecol 198(546):e541–e544